

91-045935/07

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GLAX 10.08.97

GUADIX INC

EP-412814-A1

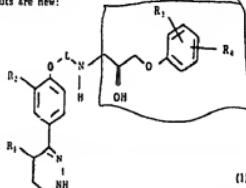
01.09.1991 US-402179 (+US-392232) (13.02.91) A61k-31/50

CD6-227-04

New pyridazine derivs. - have beta blocking activity for treatment of congestive heart failure.

C61-019437 RIAT BE CH DE DK ES FR GB GR IT LU NL SEI

Pyridazine derivs. of formula (I) and their acid addin salts are new:



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 $R_1 = H$ or lower alkyl; $R_2 = H$, halo, C_F , CN, lower alkyl or lower alkoxy;L = O, $(R_4R_5)_nCONH(R_6)C_6H_{4-n}O$ ($n = 0, 1$) or $(C_6H_4O)_p$ ($p = 1, 2$); $R_3 = R_4 = H$ or lower alkyl;

n = 1-3;

p = 2-6;

 $R_1, R_2 = H$, alkoxy, morpholine, CN, halo, C_F , alkyl, alkylsulphonyl, alkoxyalkyl, cycloalkylalkoxyalkyl, NO_2 , OH, alkenyloxy, NH₂ or mono- or di-alkylamino.**MORE SPECIFICALLY** $R_1 = H$ or Me; $R_2 = H$ or Cl;

L = (a);

n = 1 or 3;

 $R_1 = R_2 = H$; $R_1R_2 = H$ or Me; $R_3 = H$; $R_4 = CN, Cl$ or Me .

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USE(I) are useful for treating congestive heart failure. In tests (I) exhibit inotropic and β -adrenergic blocking activity. Dose is 0.1-5 mg/kg 1-4 times a day.**SPECIFICALLY CLAIMED**

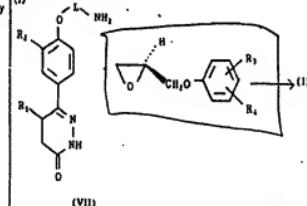
4 Compounds of formula (I) where:
 6-(4-(N-(2-(1-cyanoethoxy)-1-hydroxypropyl)amino)-2-methylpropyl)pyridazinethoxy-5-chlorophenyl)-4,5-dihydro-2(H)-pyridazinones; and
 6-(4-(N-(2-(1-(2-cyanoethoxy)-(2S)-1-hydroxypropyl)amino)ethylcarbamoyloxypropoxy-3-chlorophenyl)-4,5-dihydro-2(H)-pyridazinone.

WIDER DISCLOSURE

Intermediates of formula (VII) (see 'Starting Materials') and (VIII) (see 'Preparation') are new.

PREPARATION

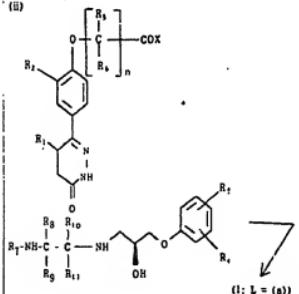
(I)



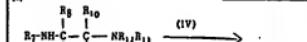
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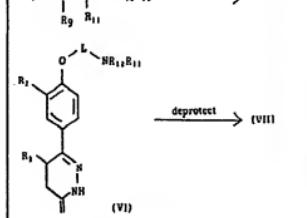
(II)

**STARTING MATERIALS**

(I)



→ (IV)



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$R_{11} = H$;
 $R_{11} =$ amino protecting gp.;
or $R_{11} + R_{11} =$ divalent amino protecting gp.

EXAMPLE

A soln. of 499 mg 6-(4-(2-aminoethylcarbamoyl)-methoxy)phenyl-5-methyl-4,5-dihydro-1(1H)-pyridazinone and 393 mg (25) (+)-3-phenoxy-1,2-epoxyp propane in 10 ml MeCN is refluxed for 10 hr. then evapd. The residue is taken up in CHCl₃/MeOH (1:1) (10ml) then flash chromatographed on gel eluting with CHCl₃/MeOH (9:1; 150 ml) then CHCl₃/MeOH/NH₃/OH (90:10:2) (1 l) to give 432 mg (60%) 6-(4-(N-(2-(3-phenoxy-2-hydroxypropyl)anilolethyl)carbamoylmethoxyphenyl)-5-methyl-4,5-dihydro-1(1H)-pyridazinone (1a).

This is dissolved in 15 ml EtOAc. 5 ml ether are added. 12 ml 0.1 M Maleic acid in ether are added with stirring. The ppt. is filtered, washed with ether and dried overnight at 50°C in vacuo to give (1a) maleate, m.p. 58-73°C (53ppg85EDWng0f0/0).

(E) ISR: No Search Report.

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